

PRELIMINARY AMENDMENT

Divisional Application of

U.S. Appln. No. 09/937,224

**AMENDMENTS TO THE CLAIMS**

**This listing of claims will replace all prior versions and listings of claims in the application:**

**LISTING OF CLAIMS:**

1-38 (Cancelled).

39. (New) A method of producing an implant loaded with a pharmaceutical active comprising the steps:

a) providing a coated implant having a coating of cross-linked water-swellaable polymer matrix on its external surface, the cross-linked water-swellaable polymer matrix comprising a polymer having pendant zwitterionic groups and pendant cationic groups, the coating having a dry thickness of at least 0.1  $\mu\text{m}$ ; and

b) contacting the coated implant with a solution or dispersion of a pharmaceutical active in a solvent whereby the pharmaceutical active is absorbed into or adsorbed onto the polymer matrix.

40. (New): A method according to claim 39 in which the said solvent is selected for its ability to swell the polymer matrix and in step b) the solvent partially swells the said polymer matrix.

41. (New): A method according to claim 39 in which the said solvent is aqueous.

42. (New) A method according to claim 39 in which the solvent is organic and which additionally comprises, following step b) a step:

c) drying the treated implant to remove the solvent.

PRELIMINARY AMENDMENT

Divisional Application of

U.S. Appln. No. 09/937,224

43. (New): A method according to claim 42 in which the removal is by evaporation.
44. (New): A method according to claim 39 in which the step b) of contacting the coated implant involves dipping the implant into a volume of the said solution or dispersion.
45. (New): A method according to claim 39 in which the implant is a stent.
46. (New): A method according to claim 45 in which the stent is mounted on a delivery device prior to said contacting step b).
47. (New): A method according to claim 44 in which step b) lasts at least 30s.
48. (New): A method according to claim 39 in which step a) comprises the sub-steps:-
- a i) providing an uncoated implant;
  - a ii) coating the implant with a cross-linkable polymer; and
  - a iii) cross-linking the cross-linkable polymer to form the said cross-linked water-swellaable polymer matrix.
49. (New): A method according to claim 41 in which the pharmaceutical active is a nucleic acid.
50. (New): A method according to claim 41 in which the pharmaceutical active is a protein which is anionically charged at physiological pH.
51. (New): A method according to claim 50 in which the protein is an antibody or a fragment thereof.
52. (New): A method according to claim 48 in which the cross-linkable polymer is formed from ethylenically unsaturated monomers including

PRELIMINARY AMENDMENT

Divisional Application of  
U.S. Appln. No. 09/937,224

- a) a zwitterionic monomer of the formula I



wherein B is a bond or a straight or branched alkylene, alkylene-oxa-alkylene or alkylene-oligooxa-alkylene group, any of which optionally include one or more fluorine substituents;

X is an organic group having a zwitterionic moiety; and

Y is an ethylenically unsaturated polymerisable group;

- b) a cationic monomer of the formula II

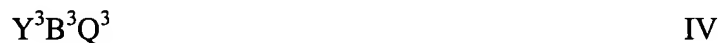


wherein  $\text{B}^1$  is a bond or a straight or branched alkylene, alkylene-oxa-alkylene or alkylene-oligooxa-alkylene group, any of which optionally includes one or more fluorine substituents;

$\text{Y}^1$  is an ethylenically unsaturated polymerisable group; and

Q is an organic group having a cationic or cationisable moiety and

- c) a crosslinkable monomer having the general formula IV:



wherein  $\text{B}^3$  is a bond or a straight or branched alkylene, alkylene-oxa-alkylene or alkylene-oligooxa-alkylene group, any of which optionally includes one or more fluorine substituents;

$\text{Y}^3$  is an ethylenically unsaturated polymerisable group; and

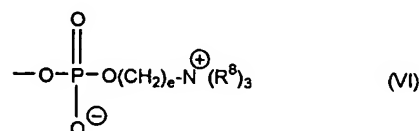
$\text{Q}^3$  is an organic group having a reactive group capable of cross-linking the polymer.

PRELIMINARY AMENDMENT

Divisional Application of  
U.S. Appln. No. 09/937,224

53. (New): A method according to claim 52 in which  $Q^3$  is a group  $SiR^4_3$  in which each  $R^4$  is a  $C_{1-4}$  alkoxy group or a halogen atom.

54. (New): A method according to claim 52 in which X is a group of formula VI



where the groups  $R^8$  are the same or different and each is hydrogen or  $C_{1-4}$  alkyl, and e is from 1 to 6.

55. (New): A method according to claim 52 in which  $Q^1$  is selected from the group consisting of  $N^+R^5_3$ ,  $P^+R^5_3$  and  $S^+R^5_2$

in which the groups  $R^5$  are the same or different and are each selected from the group consisting of hydrogen,  $C_{1-4}$ -alkyl and aryl, or two of the groups  $R^5$  together with the heteroatom to which they are attached form a saturated or unsaturated heterocyclic ring containing from 5 to 7 atoms.

56. (New): A method according to claim 52 in which the groups Y,  $Y^1$  and  $y^3$  all have the general formula  $\text{CH}_2=\text{C}(\text{R})\text{C}(\text{O})\text{A}-$  in which A is  $-\text{O}-$  or  $-\text{NR}^1$  where  $R^1$  is hydrogen or a  $C_{1-4}$  alkyl group, and R is hydrogen or a  $C_{1-4}$  alkyl group.

57. (New): A method of producing an implant loaded with a pharmaceutical active comprising the steps:

a) providing a coated implant having a coating of cross-linked water-swelling polymer matrix on its external surface, the cross-linked water-swelling polymer matrix comprising a polymer having pendant zwitterionic groups and pendant cationic groups; and

PRELIMINARY AMENDMENT

Divisional Application of  
U.S. Appln. No. 09/937,224

b) contacting the coated implant with a solution or dispersion of a pharmaceutical active which is a nucleic acid, in a solvent whereby the pharmaceutical active is absorbed into or adsorbed onto the polymer matrix.

58. (New): A method according to claim 57 in which the said solvent is selected for its ability to swell the polymer matrix and in step b) the solvent partially swells the said polymer matrix.

59. (New): A method according to claim 57 in which the said solvent is aqueous.

60. (New): A method according to claim 57 in which the solvent is organic and which additionally comprises, following step b), a step:

c) drying the treated implant to remove the solvent.

61. (New): A method according to claim 60 in which the removal is by evaporation.

62. (New): A method according to claim 57 in which the implant is a stent.

63. (New): A method according to claim 62 in which the stent is mounted on a delivery device prior to said contacting step b).

64. (New): A method according to claim 57 in which step a) comprises the sub-steps:

a i) providing an uncoated implant;

a ii) coating the implant with a cross-linkable polymer; and

a iii) cross-linking the cross-linkable polymer to form the said cross-linked water-swellaable polymer matrix.

65. (New): A method according to claim 64 in which the cross-linkable polymer is formed from ethylenically unsaturated monomers including

PRELIMINARY AMENDMENT

Divisional Application of  
U.S. Appln. No. 09/937,224

- a) a zwitterionic monomer of the formula I



wherein B is a bond or a straight or branched alkylene, alkylene-oxa-alkylene or alkylene-oligooxa-alkylene group, any of which optionally include one or more fluorine substituents;

X is an organic group having a zwitterionic moiety; and

Y is an ethylenically unsaturated polymerisable group;

- b) a cationic monomer of the formula II



wherein B<sup>1</sup> is a bond or a straight or branched alkylene, alkylene-oxa-alkylene or alkylene-oligooxa-alkylene group, any of which optionally includes one or more fluorine substituents;

Y<sup>1</sup> is an ethylenically unsaturated polymerisable group, and

Q is an organic group having a cationic or cationisable moiety and

- c) a crosslinkable monomer having the general formula IV:



wherein B<sup>3</sup> is a bond or a straight or branched alkylene, alkylene-oxa-alkylene or alkylene-oligooxa-alkylene group, any of which optionally includes one or more fluorine substituents;

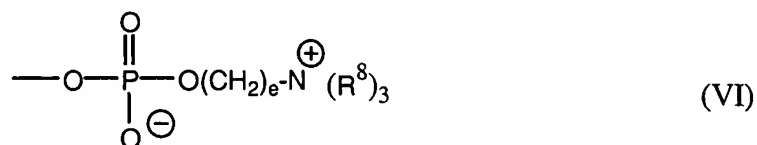
Y<sup>3</sup> is an ethylenically unsaturated polymerisable group; and

Q<sup>3</sup> is an organic group having a reactive group capable of cross-linking the polymer.

PRELIMINARY AMENDMENT  
Divisional Application of  
U.S. Appln. No. 09/937,224

66. (New): A method according to claim 65 in which  $Q^3$  is a group  $SiR^4_3$  in which  $R^4$  is a  $C_{1-4}$  alkoxy group or a halogen atom.

67. (New): A method according to claim 65 in which X is a group of formula VI



where the groups  $R^8$  are the same or different and each is hydrogen or  $C_{1-4}$  alkyl, and e is from 1 to 6.

68. (New): A method according to claim 65 in which  $Q^1$  is selected from the group consisting of  $N^+R^5_3$ ,  $P^+R^5_3$  and  $S^+R^5_2$

in which the groups  $R^5$  are the same or different and are each selected from the group consisting of hydrogen,  $C_{1-4}$ -alkyl and aryl, or two of the groups  $R^5$  together with the heteroatom to which they are attached form a saturated or unsaturated heterocyclic ring containing from 5 to 7 atoms.

69. (New): A method according to claim 65 in which the groups Y,  $Y^1$  and  $Y^3$  all have the general formula  $CH_2=C(R)C(O)A-$  in which A is  $-O-$  or  $-NR^1$  where  $R^1$  is hydrogen or a  $C_{1-4}$  alkyl group, and R is hydrogen or a  $C_{1-4}$  alkyl group.

70. (New): A method of producing an implant loaded with a pharmaceutical active comprising the steps:

PRELIMINARY AMENDMENT

Divisional Application of  
U.S. Appln. No. 09/937,224

a) providing a coated implant having a coating of cross-linked water-swella-  
ble polymer matrix on its external surface, the cross-linked water-swella-  
ble polymer matrix comprising a polymer having pendant zwitterionic groups and pendant cationic groups; and

b) contacting the coated implant with a solution or dispersion of a pharmaceutical  
active which is a protein in a solvent, the protein being anionically charged at physiological pH,  
whereby the pharmaceutical active is absorbed into or adsorbed onto the polymer matrix.

71. (New): A method according to claim 70 in which the said solvent is selected for  
its ability to swell the polymer matrix and in step b) the solvent partially swells the said polymer  
matrix.

72. (New): A method according to claim 70 in which the said solvent is aqueous.

73. (New): A method according to claim 70 in which the solvent is organic and  
which additionally comprises, following step b), a step:

c) drying the treated implant to remove the solvent.

74. (New): A method according to claim 73 in which the removal is by evaporation.

75. (New): A method according to claim 70 in which the implant is a stent.

76. (New): A method according to claim 75 in which the stent is mounted on a  
delivery device prior to said contacting step b).

77. (New): A method according to claim 70 in which step a) comprises the sub-steps:

a i) providing an uncoated implant;

a ii) coating the implant with a cross-linkable polymer; and



PRELIMINARY AMENDMENT

Divisional Application of  
U.S. Appln. No. 09/937,224

a iii) cross-linking the cross-linkable polymer to form the said cross-linked water-swellaable polymer matrix.

78. (New): A method according to claim 77 in which the cross-linkable polymer is formed from ethylenically unsaturated monomers including

- a) a zwitterionic monomer of the formula I



wherein B is a bond or a straight or branched alkylene, alkylene-oxa-alkylene or alkylene-oligooxa-alkylene group, any of which optionally include one or more fluorine substituents;

X is an organic group having a zwitterionic moiety; and

Y is an ethylenically unsaturated polymerisable group;

- b) a cationic monomer of the formula II



wherein B<sup>1</sup> is a bond or a straight or branched alkylene, alkylene-oxa-alkylene or alkylene-oligooxa-alkylene group, any of which optionally includes one or more fluorine substituents;

Y<sup>1</sup> is an ethylenically unsaturated polymerisable group, and

Q is an organic group having a cationic or cationisable moiety and

- c) a crosslinkable monomer having the general formula IV:



PRELIMINARY AMENDMENT

Divisional Application of  
U.S. Appln. No. 09/937,224

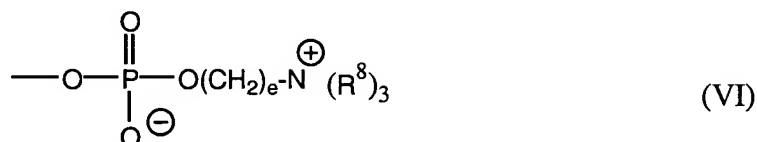
wherein  $B^3$  is a bond or a straight or branched alkylene, alkylene-oxa-alkylene or alkylene-oligooxa-alkylene group any of which optionally includes one or more fluorine substituents;

$Y^3$  is an ethylenically unsaturated polymerisable group; and

$Q^3$  is an organic group having a reactive group capable of cross-linking the polymer.

79. (New): A method according to claim 78 in which  $Q^3$  is a group  $SiR^4_3$  in which each  $R^4$  is a  $C_{1-4}$  alkoxy group or a halogen atom.

80. (New): A method according to claim 78 in which X is a group of formula VI



where the groups  $R^8$  are the same or different and each is hydrogen or  $C_{1-4}$  alkyl, and e is from 1 to 6.

81. (New): A method according to claim 78 in which  $Q^1$  is selected from the group consisting of  $N^+R^5_3$ ,  $P^+R^5_3$  and  $S^+R^5_2$

in which the groups  $R^5$  are the same or different and are each selected from the group consisting of hydrogen,  $C_{1-4}$ -alkyl and aryl, or two of the groups  $R^5$  together with the heteroatom to which they are attached form a saturated or unsaturated heterocyclic ring containing from 5 to 7 atoms.

PRELIMINARY AMENDMENT

Divisional Application of

U.S. Appln. No. 09/937,224

82. (New): A method according to claim 78 in which the groups Y, Y<sup>1</sup> and Y<sup>3</sup> all have the general formula CH<sub>2</sub>=C(R)C(O)A- in which A is -O- or -NR<sup>1</sup> where R<sup>1</sup> is hydrogen or a C<sub>1-4</sub> alkyl group, and R is hydrogen or a C<sub>1-4</sub> alkyl group.

83. (New): A method according to claim 70 in which the protein is an antibody or a fragment thereof.

84. (New): A method according to claim 39 in which the protein is an antibody or a fragment thereof.

85. (New): A method according to claim 57 in which the nucleic acid is DNA or RNA.

86. (New): A method according to claim 57 in which the nucleic acid has a molecular weight higher than 1kD.

87. (New): A method according to claim 86 in which the nucleic acid has a molecular weight higher than 1.2kD.

88. (New): A method according to claim 85 in which the nucleic acid is linear or circular and is single or double stranded.

89. (New): A method according to claim 57 in which the step b) of contacting the coated implant involves dipping the implant into a volume of the said solution or dispersion.

90. (New): A method according to claim 70 in which the step b) of contacting the coated implant involves dipping the implant into a volume of the said solution or dispersion.

91. (New): A method according to claim 57 in which step b) lasts at least 30s.

92. (New): A method according to claim 70 in which step b) lasts at least 30s.